Schmedt
785895

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	314.48	598.15

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FILE COVERS 1947 - 31 Aug 2001 VOL 135 ISS 11
FILE LAST UPDATED: 30 Aug 2001 (20010830/ED)

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E#	FREQUENCY	AT		TERM
E1	1182	10		PROLIFERATING CELL NUCLEAR ANTIGEN/CT
E2	0	2		PROLIFERATING CELL NUCLEAR ANTIGENS/CT
E3	0	1	-->	PROLIFERATION/CT
E4	2092	7		PROLIFERATION INHIBITION/CT
E5	164	2		PROLIFERATION INHIBITORS/CT

=> e e3+all/ct

```
E1            0   -->  Proliferation/CT
*********  END***

=> s e4-5
'E4' NOT FOUND
The E# entered is not currently defined.

=> e proliferation/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1        1182     10      PROLIFERATING CELL NUCLEAR ANTIGEN/CT
E2           0      2      PROLIFERATING CELL NUCLEAR ANTIGENS/CT
E3           0      1 --> PROLIFERATION/CT
E4        2092      7      PROLIFERATION INHIBITION/CT
E5         164      2      PROLIFERATION INHIBITORS/CT

=> s e4+all/ct
THE ESTIMATED SEARCH COST FOR FILE 'CAPLUS' IS 10.36 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:n
SEARCH ENDED BY USER

=> s e4-5
          2092 "PROLIFERATION INHIBITION"/CT
           164 "PROLIFERATION INHIBITORS"/CT
L1        2249 ("PROLIFERATION INHIBITION"/CT OR "PROLIFERATION
INHIBITORS"/CT)

=> e e4+all/ct
E1       34999   BT1  Cell proliferation/CT
E2        2092     -->  Proliferation inhibition/CT
                    HN   Valid heading during volume 126 (1997) to present.
E3                  UF   Antiproliferative activity/CT
E4                  UF   Cell growth arrest/CT
E5                  UF   Cell growth inhibition/CT
E6                  UF   Growth arrest/CT
E7                  UF   Inhibition of proliferation/CT
*********  END***

=> e proliferation inhibitors/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      1      PROLIFERATION/CT
E2        2092      7      PROLIFERATION INHIBITION/CT
E3         164      2 --> PROLIFERATION INHIBITORS/CT
E4           0      3      PROLIFERATION, FIBROBLAST/CT
E5           0      3      PROLIFERATION, HEPATOCYTE/CT

=> e e3+all/ct
E1         164   -->  Proliferation inhibitors/CT
                   HN   Valid heading during volumes 126-127 (1997) only.
E2                 NEW  Cell proliferation (L) inhibitors/CT
*********  END***

=> e a2badensoine receptor/cn 5
   REG1stRY INITIATED
```

```
Substance data EXPAND from CAS REGISTRY in progress...


E1            1     A2A ADENOSINE RECEPTOR (CAVIA PORCELLUS STRAIN HARTLEY
CLONE
                     GPA2R)/CN
E2            1     A2B4/CN
E3            0 --> A2BADENSOINE RECEPTOR/CN
E4            1     A2C/CN
E5            1     A2P1/CN

=> e a2b adensoine receptor/cn 5
   REG1stRY INITIATED
Substance data EXPAND from CAS REGISTRY in progress...


E1            1     A299/CN
E2            1     A2A ADENOSINE RECEPTOR (CAVIA PORCELLUS STRAIN HARTLEY
CLONE
                     GPA2R)/CN
E3            0 --> A2B ADENSOINE RECEPTOR/CN
E4            1     A2B4/CN
E5            1     A2C/CN


=> e a2b adensoine receptor/ct 5
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1         200     2     A2A RECEPTOR (ADENOSINE)/CT
E2           0     1     A2B/CT
E3           0       --> A2B ADENSOINE RECEPTOR/CT
E4          70     2     A2B RECEPTOR (ADENOSINE)/CT
E5           0     2     A2B RECEPTORS/CT

=> e e4+all/ct
E1          70   -->  A2b receptor (adenosine)/CT
                 HN   Valid heading during volumes 126-130 (1997-June 1999)
                      only.
E2               NEW  Adenosine receptors (L) A2b/CT
*********  END***

=> e proliferation inhibitor/ct 5
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           0     1     PROLIFERATION/CT
E2        2092     7     PROLIFERATION INHIBITION/CT
E3           0       --> PROLIFERATION INHIBITOR/CT
E4         164     2     PROLIFERATION INHIBITORS/CT
E5           0     3     PROLIFERATION, FIBROBLAST/CT

=> e e2+all/ct
E1       34999   BT1  Cell proliferation/CT
```

```
E2         2092      -->  Proliferation inhibition/CT
                          HN   Valid heading during volume 126 (1997) to present.
E3                        UF   Antiproliferative activity/CT
E4                        UF   Cell growth arrest/CT
E5                        UF   Cell growth inhibition/CT
E6                        UF   Growth arrest/CT
E7                        UF   Inhibition of proliferation/CT
*********  END***

=> s e1-7
          34999 "CELL PROLIFERATION"/CT
           2092 "PROLIFERATION INHIBITION"/CT
              0 "ANTIPROLIFERATIVE ACTIVITY"/CT
              0 "CELL GROWTH ARREST"/CT
              0 "CELL GROWTH INHIBITION"/CT
              0 "GROWTH ARREST"/CT
              0 "INHIBITION OF PROLIFERATION"/CT
L2        36756 ("CELL PROLIFERATION"/CT OR "PROLIFERATION INHIBITION"/CT OR
                "ANTIPROLIFERATIVE ACTIVITY"/CT OR "CELL GROWTH ARREST"/CT OR
                "CELL GROWTH INHIBITION"/CT OR "GROWTH ARREST"/CT OR
"INHIBITION
                 OF PROLIFERATION"/CT)

=> e cascular endothelial cell growth factor/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      1      CASCO/CT
E2           0      2      CASCO A/CT
E3           0        --> CASCULAR ENDOTHELIAL CELL GROWTH FACTOR/CT
E4           1            CASCUTA/CT
E5           0      1     CASE/CT

=> e vascular endothelial cell growth factor/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      2      VASCULAR DISEASES, INFLAMMATION/CT
E2           0      2      VASCULAR DISEASES, VASCULITIS/CT
E3           0        --> VASCULAR ENDOTHELIAL CELL GROWTH FACTOR/CT
E4           0      2      VASCULAR ENDOTHELIAL CELL GROWTH FACTOR RECEPTORS/CT
E5           0      3      VASCULAR ENDOTHELIAL GROWTH FACTOR/CT

=> e e4+all/ct
E1           0    -->  Vascular endothelial cell growth factor receptors/CT
E2         855      USE  Vascular endothelial growth factor receptors/CT
*********  END***

=> s e2
L3         855 "VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS"/CT

=> e vascular bed endothelial cell/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      2      VASCULAR ANTICOAGULANT .BETA. LIPOCORTINS/CT
E2           0      2      VASCULAR ANTICOAGULANTS BLOOD-COAGULATION FACTORS/CT
E3           0        --> VASCULAR BED ENDOTHELIAL CELL/CT
```

```
E4            0      2      VASCULAR BUNDLE PLANT TISSUE/CT
E5            0      2      VASCULAR CANCER/CT

=> e endothelial cell/ct 5
E#   FREQUENCY    AT      TERM
--   ---------    --      ----
E1           18      2      ENDOTAXY/CT
E2            0      1      ENDOTHELIAL/CT
E3            0      2 --> ENDOTHELIAL CELL/CT
E4            0      2      ENDOTHELIAL CELL-DERIVED GROWTH FACTORS/CT
E5          114      2      ENDOTHELIAL INJURY (VASCULAR)/CT

=> fil medl,caplus,biosis,embase,wpids,jicst
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    15.04     618.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -22.93

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=> s (l1 or l2 or prolifer? inhibit? or cell prolifer?(l)inhibit?) and (a2b
receptor (a) adenosine or adensoine receptor!(l)a2b or a2b)
L4             7 FILE MEDLINE
L5            14 FILE CAPLUS
L6            10 FILE BIOSIS
L7             8 FILE EMBASE
L8             1 FILE WPIDS
L9             0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L10           40 (L1 OR L2 OR PROLIFER? INHIBIT? OR CELL PROLIFER?(L) INHIBIT?)
                 AND (A2B RECEPTOR (A) ADENOSINE OR ADENSOINE RECEPTOR!(L) A2B
                 OR A2B)

=> s l10 and (vascular endothelial cell! or coronary endothelial cell! or
endothelial(l)vascular)
```

L11 0 FILE MEDLINE
L12 1 FILE CAPLUS
L13 1 FILE BIOSIS
L14 0 FILE EMBASE
L15 0 FILE WPIDS
L16 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L17 2 L10 AND (VASCULAR ENDOTHELIAL CELL! OR CORONARY ENDOTHELIAL CELL! OR ENDOTHELIAL(L) VASCULAR)

=> dup rem l17
PROCESSING COMPLETED FOR L17
L18 1 DUP REM L17 (1 DUPLICATE REMOVED)

=> d cbib abs

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
1999:666894 Document No. 131:318275 Adenosine receptor activation induces **vascular endothelial** growth factor in human retinal **endothelial** cells. Grant, Maria B.; Tarnuzzer, Roy W.; Caballero, Sergio; Ozeck, Mark J.; Davis, Margaret I.; Spoerri, Polyxenie E.; Feoktistov, Igor; Biaggioni, Italo; Shryock, John C.; Belardinelli, Luiz (Departments of Medicine, University of Florida, Gainesville, FL, 32610-0226, USA). Circ. Res., 85(8), 699-706 (English) 1999. CODEN: CIRUAL. ISSN: 0009-7330. Publisher: Lippincott Williams & Wilkins.
AB Adenosine, released in increased amts. by hypoxic tissues, is thought to be an angiogenic factor that links altered cellular metab. caused by oxygen deprivation to compensatory angiogenesis. Adenosine interacts with 4 subtypes of G protein-coupled receptors, termed A1, A2A, **A2B**, and A3. The authors investigated whether adenosine causes proliferation of human retinal **endothelial** cells (HRECs) and synthesis of **vascular endothelial** growth factor (VEGF) and, if so, which adenosine receptor subtype mediates these effects. The nonselective adenosine receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA), in a concn.-dependent manner, increased both VEGF mRNA and protein expression by HRECs, as well as proliferation. This proliferative effect of NECA was **inhibited** by the addn. of anti-human VEGF antibody. NECA also increased insulin-like growth factor-I and basic fibroblast growth factor mRNA expression in a time-dependent manner and cAMP accumulation in these cells. In contrast, neither the A1 agonist N6-cyclopentyladenosine nor the A2A agonist 2-p-(2-carboxyethyl) phenethylamino-NECA caused any of the above effects of NECA. The effects of NECA were not significantly attenuated by either the A2A antagonist SCH58261 or the A1 antagonist 8-cyclopentyl-1,3-dipropylxanthine. However, the nonselective adenosine receptor antagonist xanthine amine congener completely **inhibited** the effects of NECA. Addn. of antisense oligonucleotide complementary to **A2B** adenosine receptor mRNA **inhibited** VEGF protein prodn. by HRECs after NECA stimulation. Thus, the **A2B** adenosine receptor subtype appears to mediate the actions of adenosine to increase growth factor prodn., cAMP content, and **cell**

proliferation of HRECs. Adenosine activates the **A2B** adenosine receptor in HRECs, which may lead to neovascularization by a mechanism involving increased angiogenic growth factor expression.

```
=> s l10 not l17
L19           7 FILE MEDLINE
L20          13 FILE CAPLUS
L21           9 FILE BIOSIS
L22           8 FILE EMBASE
L23           1 FILE WPIDS
L24           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L25          38 L10 NOT L17

<------User Break------>
u
SEARCH ENDED BY USER
SEARCH ENDED BY USER

=> s (tumour or tumor or retin? or derm? or brain or cell growth factor or
vegf or l3) and l25
L26           3 FILE MEDLINE
L27           3 FILE CAPLUS
L28           4 FILE BIOSIS
L29           1 FILE EMBASE
L30           0 FILE WPIDS
L31           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L32          11 (TUMOUR OR TUMOR OR RETIN? OR DERM? OR BRAIN OR CELL GROWTH
                FACTOR OR VEGF OR L3) AND L25

=> s l25 and (coronary or heart)
L33           0 FILE MEDLINE
L34           1 FILE CAPLUS
L35           0 FILE BIOSIS
L36           1 FILE EMBASE
L37           0 FILE WPIDS
L38           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L39           2 L25 AND (CORONARY OR HEART)

=> s l32 or l39
L40           3 FILE MEDLINE
L41           4 FILE CAPLUS
L42           4 FILE BIOSIS
L43           2 FILE EMBASE
L44           0 FILE WPIDS
L45           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L46          13 L32 OR L39
```

=> s l46 and (oral? or nasal? or transderm? or bolus or intraven? or eye drops or inhal? or micropump?)
L47 0 FILE MEDLINE
L48 1 FILE CAPLUS
L49 1 FILE BIOSIS
L50 0 FILE EMBASE
L51 0 FILE WPIDS
L52 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L53 2 L46 AND (ORAL? OR NASAL? OR TRANSDERM? OR BOLUS OR INTRAVEN? OR
EYE DROPS OR INHAL? OR MICROPUMP?)

=> dup rem l53
PROCESSING COMPLETED FOR L53
L54 1 DUP REM L53 (1 DUPLICATE REMOVED)

=> d cbib abs ;s l46 not l53

L54 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
2001:383911 Resistance of muscle to **tumor** metastases: A role for A3 adenosine receptor agonists. Bar-Yehuda, Sara; Barer, Faina; Volfsson, Lea; Fishman, Pnina (Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel-Aviv University, Petach Tikva, Israel). Neoplasia (N. Y., NY, U. S.), 3(2), 125-131 (English) 2001. CODEN: NEOPFL. ISSN: 1522-8002. Publisher: Nature America Inc..

AB **Tumor** metastases are extremely rare in striated muscles. Lately, we have found that muscle cell conditioned medium (MCM) **inhibits** the proliferation of various **tumor** cells while maintaining the growth of normal murine bone marrow cells. This dual activity was confirmed in vivo when the MCM was administered **orally**, i.e., it **inhibited** the development of **tumor** growth in mice and prevented the myelotoxic effects of chemotherapy. Adenosine was found to be one of the active components of MCM, **inhibiting tumor** cell growth while maintaining bone marrow **cell proliferation** in vitro. Adenosine is known to act as an important regulatory mol. through its binding to specific G-protein-assocd. A1, A2a, **A2b** and A3 cell surface receptors. In distinction from MCM, adenosine did not suppress **tumor** development in mice and was not active as a chemoprotective agent when administered **orally** or i.v. Thus, the in vivo activity of MCM could not be attributed to adenosine. In this study, MCM from which adenosine was enzymically removed still retained its dual activity that was also found to be mediated through the A3 adenosine receptor (A3AR). This result led to the conclusion that natural agonists to A3AR were responsible for the activity of MCM. We further tested synthetic agonist to the A3AR and demonstrated that it possessed the same in vitro and in vivo activity profile as MCM. Taken together, muscle cells, in addn. to adenosine, secrete natural agonists to A3AR. These agonists are stable nondegradable mols. and may contribute to the systemic

anticancer and chemoprotective activity exerted by MCM. This group of mols. may account for the rarity of **tumor** metastases in muscle.

L55 3 FILE MEDLINE
L56 3 FILE CAPLUS
L57 3 FILE BIOSIS
L58 2 FILE EMBASE
L59 0 FILE WPIDS
L60 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L61 11 L46 NOT L53

=> dup rem l61
PROCESSING COMPLETED FOR L61
L62 7 DUP REM L61 (4 DUPLICATES REMOVED)

=> d cbib abs 1-7;s grant, m?/au,in or grant m?/au,in;s belardinelli, l?/au,in or belardinelli l?/au,in

L62 ANSWER 1 OF 7 MEDLINE DUPLICATE 1
2001433635 Document Number: 21374019. PubMed ID: 11481274.
Proliferation,
migration, and ERK activation in human **retinal** endothelial cells through A(2B) adenosine receptor stimulation. Grant M B; Davis M I; Caballero S; Feoktistov I; Biaggioni I; Belardinelli L. (Department of Medicine, University of Florida, Gainesville 32610-0267, USA.. grantma@pharmacology.ufl.edu) . INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (2001 Aug) 42 (9) 2068-73. Journal code: GWI; 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: The nucleoside adenosine has been implicated in angiogenesis. A previous study demonstrated that activation of the A(2B) adenosine receptor (AdoR) increases cAMP accumulation, **cell proliferation**, and **VEGF** expression in human **retinal** endothelial cells (HRECs). In the present study, the role of this receptor was further characterized by examination of the effects of the selective A(2B) AdoR antagonists 3-N-propylxanthine (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX) on AdoR-mediated HREC proliferation, capillary tube formation, and signal-transduction pathways.

METHODS: HRECs were exposed to the adenosine analogue 5'-N-ethylcarboxamido-adenosine (NECA) in the absence or presence of AdoR antagonists. Migration was measured using Boyden chambers. Proliferation was assessed by counting cells. Western analysis was used to assess extracellular signal-related kinase (ERK) and cAMP response element-binding protein (CREB) in cell lysates. The effect of AdoR activation on tube formation was studied using cells grown on a synthetic basement membrane matrix. RESULTS: NECA induced proliferation in a concentration-dependent manner that was **inhibited** by enprofylline and IPDX. NECA stimulated chemotaxis in a concentration-dependent manner that was also blocked by both A(2B) AdoR antagonists. NECA activated ERK and CREB in HRECs. Both A(2B) AdoR antagonists diminished activation of ERK by NECA exposure. ERK activation

was also blocked by the ERK-mitogen-activated protein kinase (MAPK) **inhibitor** PD98059, but not by the protein kinase A (PKA) **inhibitor** H-89. CREB activation was blocked by H-89, but not by PD98059, suggesting that ERK activation is independent of PKA. NECA enhanced tube formation on the matrix, whereas both A(2B) AdoR antagonists attenuated this effect. CONCLUSIONS: The selective A(2B) AdoR antagonists, enprofylline and IPDX, **inhibited** NECA-stimulated proliferation, ERK activation, cell migration, and capillary tube formation. A(2B) AdoR **inhibition** may offer a way to **inhibit retinal** angiogenesis and provide a novel therapeutic approach to treatment of diseases associated with aberrant neovascularization, such as diabetic **retinopathy** and **retinopathy** of prematurity.

L62 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
2001:180800 Document No. 134:232144 **A2B** receptors mediate the antimitogenic effects of adenosine in cardiac fibroblasts. Dubey, Raghvendra K.; Gillespie, Delbert G.; Zacharia, Lefteris C.; Mi, Zaichuan; Jackson, Edwin K. (Center for Clinical Pharmacology, Departments of Medicine and Pharmacology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA). Hypertension, 37(2, Pt. 2), 716-721 (English) 2001.
CODEN: HPRTDN. ISSN: 0194-911X. Publisher: Lippincott Williams & Wilkins.

AB Adenosine **inhibits** growth of cardiac fibroblasts; however, the adenosine receptor subtype that mediates this antimitogenic effect remains undefined. Therefore, the goals of this study were to det. which adenosine receptor subtype mediates the antimitogenic effects of adenosine and to investigate the signal transduction mechanisms involved. In rat left ventricular cardiac fibroblasts, PDGF-BB (25 ng/mL) stimulated DNA synthesis (3H-thymidine incorporation), cellular proliferation (cell no.), collagen synthesis (3H-proline incorporation), and MAP kinase activity. The adenosine receptor agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N6-cyclopentyladenosine, 4-aminobenzyl-5'-N-methylcarboxamidoadenosine, or CGS 21680, **inhibited** the growth effects of PDGF-BB, an agonist profile consistent with an **A2B** receptor-mediated effect. The adenosine receptor antagonists KF 17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-**inhibitory** effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an antagonist profile consistent with an A2 receptor-mediated effect. Antisense, but not sense or scrambled, oligonucleotides to the **A2B** receptor stimulated basal and PDGF-induced DNA synthesis, **cell proliferation**, and collagen synthesis. Moreover, the growth-**inhibitory** effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl)adenine plus iodotubericidin (**inhibitors** of adenosine deaminase and adenosine kinase, resp.) were abolished by antisense, but not scrambled or sense, oligonucleotides to the **A2B** receptor. Our findings strongly support the

hypothesis that adenosine causes **inhibition** of cardiac fibroblast growth by activating **A2B** receptors coupled to **inhibition** of MAP kinase activity. Thus, **A2B** receptors may play a crit. role in regulating cardiac remodeling assocd. with cardiac fibroblast proliferation. Pharmacol. or mol. biol. activation of **A2B** receptors may prevent cardiac remodeling assocd. with hypertension, myocardial infarction, and myocardial reperfusion injury after ischemia.

L62 ANSWER 3 OF 7 MEDLINE DUPLICATE 3

2001091226 Document Number: 21023319. PubMed ID: 11147810. Differential effect of adenosine on **tumor** and normal cell growth: focus on the A3 adenosine receptor. Ohana G; Bar-Yehuda S; Barer F; Fishman P. (Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Tel-Aviv University, Petach-Tikva, Israel.) JOURNAL OF CELLULAR PHYSIOLOGY, (2001 Jan) 186 (1) 19-23. Ref: 47. Journal code: HNB. ISSN: 0021-9541. Pub. country: United States. Language: English.

AB Adenosine is an ubiquitous nucleoside present in all body cells. It is released from metabolically active or stressed cells and subsequently acts as a regulatory molecule through binding to specific A1, A2A, **A2B** and A3 cell surface receptors. The synthesis of agonists and antagonists to the adenosine receptors and their cloning enabled the exploration of their physiological functions. As nearly all cells express specific adenosine receptors, adenosine serves as a physiological regulator and acts as a cardioprotector, neuroprotector, chemoprotector, and as an immunomodulator. At the cellular level, activation of the receptors by adenosine initiates signal transduction mechanisms through G-protein associated receptors. Adenosine's unique characteristic is to differentially modulate normal and transformed cell growth, depending upon its extracellular concentration, the expression of adenosine cell surface receptors, and the physiological state of the target cell. Stimulation of **cell proliferation** following incubation with adenosine has been demonstrated in a variety of normal cells in the range of low micromolar concentrations, including mesangial and thymocyte cells, Swiss mouse 3T3 fibroblasts, and bone marrow cells. Induction of apoptosis in **tumor** or normal cells was shown at higher adenosine concentrations (>100 microM) such as in leukemia HL-60, lymphoma U-937, A431 epidermoid cells, and GH3 **tumor** pituitary cell lines. It was further noted that the A3 adenosine receptor (A3AR) plays a key role in the **inhibitory** and stimulatory growth activities of adenosine. Modulation of the A3AR was found to affect cell growth either positively or negatively depending on the concentration of the agonist, similar to the effect described for adenosine. At nanomolar concentrations, the A3AR agonists possess dual activity, i.e., antiproliferative activity toward **tumor** cells and stimulatory effect on bone marrow cells. In vivo, these agonists exerted anti-cancer effects, and when given in combination with chemotherapy, they enhanced the chemotherapeutic index and acted as chemoprotective agents. Taken together, activation of the A3AR, by minute concentrations of its natural ligand or synthetic agonists, may serve as a new approach for cancer therapy.

L62 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS

1999:269659 Document No. 131:40083 Adenosine prevents the death of mesencephalic dopaminergic neurons by a mechanism that involves astrocytes. Michel, Patrick P.; Marien, Marc; Ruberg, Merle; Colpaert, Francis; Agid, Yves (INSERM U. 289, Hopital de la Salpetriere, Paris, 75654, Fr.). J. Neurochem., 72(5), 2074-2082 (English) 1999. CODEN: JONRA9. ISSN: 0022-3042. Publisher: Lippincott Williams & Wilkins.

AB The purinergic nucleoside adenosine effectively prevented the death of dopaminergic neurons that occurs spontaneously and progressively in cultures of rat mesencephalon. Adenosine also significantly increased dopamine uptake, attesting to the state of differentiation and functional integrity of the neurons that were rescued. The effects of adenosine were (a) specific to the dopaminergic neurons in these cultures, (b) long-lived, (c) still obsd. when the treatment was delayed after plating, (d) potentiated by inhibition of adenosine deaminase, and (e) abolished when this enzyme was added in excess to the culture medium. The action of adenosine was mimicked by 5'-(N-ethylcarboxamido)adenosine and dibutyryl-cAMP, but not by CGS-21680, suggesting the possible involvement of **A2B** subtype purinergic receptors. ATP was also neuroprotective, but its action resulted principally from conversion to adenosine by ectonucleotidases. Several anticancer drugs, including cytosine arabinoside, have been shown previously to prevent apoptosis in cultured dopaminergic neurons by a mechanism that requires the inhibition of proliferating astrocytes. In the presence of adenosine, astrocytes were more differentiated, and their proliferation rate was significantly reduced, suggesting that the neurotrophic effect of the adenine nucleoside resulted also from the repression of the astroglial cells. The authors did not find evidence of a trophic intermediary in adenosine-treated cultures, however, leading to the hypothesis that limitation of astrocyte replication in itself and/or ensuing changes in the glial phenotype were crucial. The authors' results suggest that mols. that modulate adenine nucleotide/nucleoside release may be useful for the treatment of chronic neurodegenerative conditions affecting dopaminergic neurons, such as Parkinson's disease.

L62 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

1999:109305 Document No.: PREV199900109305. In vivo **tumor** suppression by adenovirus-mediated interferon alpha2b gene delivery. Ahmed, C. M. Iqbal; Sugarman, Barry J.; Johnson, Duane E.; Bookstein, Robert E.; Saha, Deba P.; Nagabhushan, T. L.; Wills, Ken N. (1). (1) Canji Inc., 3030 Science Park Rd., Suite 302, San Diego, CA 92121 USA. Human Gene Therapy, (Jan. 1, 1999) Vol. 10, No. 1, pp. 77-84. ISSN: 1043-0342. Language: English.

AB A replication-deficient adenovirus encoding human interferon **a2b**, driven by the human cytomegalovirus (CMV) promoter, was constructed and characterized. This construct was used to infect human cells derived from different types of cancer. The production of protein and its secretion into the culture medium were tested by Western blotting and immunoassay. **Inhibition** of **cell proliferation** and antiviral activity, two of the most important biological activities of interferon, were observed with this construct. PC-3 cells, derived from human prostatic cancer, or Hep3B cells, derived from human hepatocellular

carcinoma, were injected subcutaneously to generate and establish in vivo **tumors** in athymic nude mice. Intratumoral injection with the recombinant adenovirus expressing interferon **a2b** resulted in complete regression of **tumor** growth. Our results demonstrate that interferon gene delivery using recombinant adenoviral vectors may be a useful approach to treat a variety of cancers.

L62 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
1994:502401 Document No.: PREV199497515401. Effects of type I-interferons on human thyroid epithelial cells derived from normal and **tumour** tissue. Selzer, Edgar; Wilfing, Astrid; Sexl, Veronika; Freissmuth, Michael (1). (1) Inst. Pharmacol., Univ. Vienna, Waehringer Strasse 13a, A-1090 Vienna Austria. Naunyn-Schmiedeberg's Archives of Pharmacology, (1994) Vol. 350, No. 3, pp. 322-328. ISSN: 0028-1298. Language: English.
AB Long term interferon (IFN) therapy is frequently associated with side effects which affect the thyroid gland such as hypothyroidism and thyroiditis. We have therefore tested the ability of type I-IFNs to exert direct effects on primary cultures of human thyroid epithelial cells: (i) Type I-IFNs (IFN-alpha-2b and IFN-omega) **inhibit cell proliferation** as determined by (3H)thymidine incorporation with a half-maximal effect at apprx 1 ng/ml (50 pM). **Inhibition** of cell growth is observed in cells derived from normal thyroid as well as neoplastic tissue (autonomous and non-secreting adenoma; follicular, papillary and anaplastic carcinoma). (ii) Over a similar concentration range, type I-IFNs suppressed thyroglobulin release by thyroid cells. (iii) IFN-**a2b** stimulated surface expression of major histocompatibility class (MHC) I but not MHC II molecules, while IFN-gamma enhanced the expression of both MHC I and MHC II molecules. This effect of IFN-gamma, but not that of IFN-**a2b** was antagonized by suramin. (iv) Incubation of thyroid cells with IFN-alpha-2b also resulted in increased cell surface levels of the intercellular adhesion molecule I (ICAM-1). These findings demonstrate that type I-IFNs directly affect thyroid function and explain related side effects of these cytokines. In addition, our results provide a rational basis for the possible use of type I-IFNs in the treatment of patients with advanced thyroid cancer for whom no therapeutic alternative exists.

L62 ANSWER 7 OF 7 MEDLINE
94058094 Document Number: 94058094. PubMed ID: 8239523.
Inhibition of human glioma **cell proliferation** and glutathione S-transferase by ascorbyl esters and interferon. Naidu A K; Wiranowska M; Kori S H; Prockop L D; Kulkarni A P. (Department of Neurology, College of Medicine, University of South Florida, Tampa 33612.) ANTICANCER RESEARCH, (1993 Sep-Oct) 13 (5A) 1469-75. Journal code: 59L; 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.
AB The in vitro effect of ascorbyl esters (ascorbyl-stearate [As-S] and -palmitate [As-P]) and interferon (recombinant human interferon-**a2b** [rHuIFN-**a2b**]) on human glioma (U-373) **cell proliferation**, viability and glutathione-S-transferase (GST) activity was studied. The effect of As-S, As-P and rHuIFN-**a2b** on **cell proliferation** and viability was evaluated by [3H] Thymidine incorporation and colorimetric MTT assays, respectively.

Incubation of glioma cells with As-S, As-P or rHuIFN-**a2b** for 24 h resulted in a dose dependent **inhibition** of **cell proliferation** (IC50 = 68.0 microM As-S, 86.0 microM As-P and 47.3 Units/ml rHuIFN-**a2b**), and moderate decrease of cell viability. It was found that As-S was a more efficient **inhibitor** of **cell proliferation**, viability and GST activity than As-P. GST from U-373 cells was purified. The activity of purified GST towards 1-chloro-2,4-dinitrobenzene (CDNB) was **inhibited** in a dose dependent manner by ascorbyl esters (I-50 = 27.5 microM As-S and 56.0 microM As-P) but not by rHuIFN-**a2b**. GST activity of cytosol isolated from U-373 cells which were previously treated with As-S (150 microM) or rHuIFN-**a2b** (150 units/ml) for 0, 2, 5, 10, 20 and 30 min was sharply decreased during 5 to 10 min of treatment and increased at longer durations of treatment.

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'IN' IS NOT A VALID FIELD CODE
L63         659 FILE MEDLINE
L64         580 FILE CAPLUS
L65         811 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L66         476 FILE EMBASE
L67          77 FILE WPIDS
L68           4 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L69        2607 GRANT, M?/AU,IN OR GRANT M?/AU,IN


'IN' IS NOT A VALID FIELD CODE
L70         135 FILE MEDLINE
L71         191 FILE CAPLUS
L72         283 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L73         145 FILE EMBASE
L74          10 FILE WPIDS
L75           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L76         764 BELARDINELLI, L?/AU,IN OR BELARDINELLI L?/AU,IN

=> s l69 and l76
L77           2 FILE MEDLINE
L78           2 FILE CAPLUS
L79           4 FILE BIOSIS
L80           2 FILE EMBASE
L81           0 FILE WPIDS
L82           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L83          10 L69 AND L76
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L84 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2001 ACS
2001:617805 Method for identifying and using a2b adenosine receptor antagonists to mediate mammalian cell proliferation. **Belardinelli, Luiz**; Grant, Maria B. (CV Therapeutics, Inc., USA; University of Florida Research Foundation, Inc.). PCT Int. Appl. WO 2001060350 A2 20010823, 17 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4917 20010216. PRIORITY: US 2000-PV183141 20000217.
AB This invention concerns methods for identifying A2B adenosine receptor agonists and antagonists as well as methods for using A2B adenosine receptor antagonists to treat cell proliferation orders mediated by the A2B adenosine receptor.

L84 ANSWER 2 OF 6 MEDLINE DUPLICATE 1
2001433635 Document Number: 21374019. PubMed ID: 11481274.
Proliferation,
migration, and ERK activation in human retinal endothelial cells through A(2B) adenosine receptor stimulation. **Grant M B**; Davis M I; Caballero S; Feoktistov I; Biaggioni I; **Belardinelli L.** (Department of Medicine, University of Florida, Gainesville 32610-0267, USA.. grantma@pharmacology.ufl.edu) . INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (2001 Aug) 42 (9) 2068-73. Journal code: GWI; 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.
AB PURPOSE: The nucleoside adenosine has been implicated in angiogenesis. A previous study demonstrated that activation of the A(2B) adenosine receptor (AdoR) increases cAMP accumulation, cell proliferation, and VEGF expression in human retinal endothelial cells (HRECs). In the present study, the role of this receptor was further characterized by examination of the effects of the selective A(2B) AdoR antagonists 3-N-propylxanthine (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX) on AdoR-mediated HREC proliferation, capillary tube formation, and signal-transduction pathways. METHODS: HRECs were exposed to the adenosine analogue 5'-N-ethylcarboxamido-adenosine (NECA) in the absence or presence of AdoR antagonists. Migration was measured using Boyden chambers. Proliferation was assessed by counting cells. Western analysis was used to assess extracellular signal-related kinase (ERK) and cAMP response element-binding protein (CREB) in cell lysates. The effect of AdoR activation on tube formation was studied using cells grown on a synthetic basement membrane matrix. RESULTS: NECA induced proliferation in a concentration-dependent manner that was inhibited by enprofylline and

IPDX. NECA stimulated chemotaxis in a concentration-dependent manner that was also blocked by both A(2B) AdoR antagonists. NECA activated ERK and CREB in HRECs. Both A(2B) AdoR antagonists diminished activation of ERK by NECA exposure. ERK activation was also blocked by the ERK-mitogen-activated protein kinase (MAPK) inhibitor PD98059, but not by the protein kinase A (PKA) inhibitor H-89. CREB activation was blocked by H-89, but not by PD98059, suggesting that ERK activation is independent of PKA. NECA enhanced tube formation on the matrix, whereas both A(2B) AdoR antagonists attenuated this effect. CONCLUSIONS: The selective A(2B) AdoR antagonists, enprofylline and IPDX, inhibited NECA-stimulated proliferation, ERK activation, cell migration, and capillary tube formation. A(2B) AdoR inhibition may offer a way to inhibit retinal angiogenesis and provide a novel therapeutic approach to treatment of diseases associated with aberrant neovascularization, such as diabetic retinopathy and retinopathy of prematurity.

L84 ANSWER 3 OF 6 MEDLINE DUPLICATE 2

1999451092 Document Number: 99451092. PubMed ID: 10521243. Adenosine receptor activation induces vascular endothelial growth factor in human retinal endothelial cells. **Grant M B**; Tarnuzzer R W; Caballero S; Ozeck M J; Davis M I; Spoerri P E; Feoktistov I; Biaggioni I; Shryock J C; **Belardinelli L**. (Department of Medicine, Opnthalmology and Pharmacology, University of Florida, Gainesville, Fla 32610-0226, USA.. grantma@medicine.ufl.edu) . CIRCULATION RESEARCH, (1999 Oct 15) 85 (8) 699-706. Journal code: DAJ; 0047103. ISSN: 1524-4571. Pub. country: United States. Language: English.

AB Adenosine, released in increased amounts by hypoxic tissues, is thought to be an angiogenic factor that links altered cellular metabolism caused by oxygen deprivation to compensatory angiogenesis. Adenosine interacts with 4 subtypes of G protein-coupled receptors, termed A(1), A(2A), A(2B), and A(3). We investigated whether adenosine causes proliferation of human retinal endothelial cells (HRECs) and synthesis of vascular endothelial growth factor (VEGF) and, if so, which adenosine receptor subtype mediates these effects. The nonselective adenosine receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA), in a concentration-dependent manner, increased both VEGF mRNA and protein expression by HRECs, as well as proliferation. This proliferative effect of NECA was inhibited by the addition of anti-human VEGF antibody. NECA also increased insulin-like growth factor-I and basic fibroblast growth factor mRNA expression in a time-dependent manner and cAMP accumulation in these cells. In contrast, neither the A(1) agonist N(6)-cyclopentyladenosine nor the A(2A) agonist 2-p-(2-carboxyethyl) phenethylamino-NECA caused any of the above effects of NECA. The effects of NECA were not significantly attenuated by either the A(2A) antagonist SCH58261 or the A(1) antagonist 8-cyclopentyl-1, 3-dipropylxanthine. However, the nonselective adenosine receptor antagonist xanthine amine congener completely inhibited the effects of NECA. Addition of antisense oligonucleotide complementary to A(2B) adenosine receptor mRNA inhibited VEGF protein production by HRECs after

NECA stimulation. Thus, the A(2B) adenosine receptor subtype appears to mediate the actions of adenosine to increase growth factor production, cAMP content, and cell proliferation of HRECs. Adenosine activates the A(2B) adenosine receptor in HRECs, which may lead to neovascularization by a mechanism involving increased angiogenic growth factor expression.

L84 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
1999:244744 Document No.: PREV199900244744. Adenosine mediates human retinal endothelial cell (HREC) chemotaxis, capillary tube formation and stimulatory cell signaling cascades. **Grant, M. B. (1)**; Davis, M. I. (1); Tarnuzzer, R. W. (1); Caballero, S. (1); **Belardinelli, L. (1)**. (1) University of Florida, Gainesville, FL USA. IOVS, (March 15, 1999) Vol. 40, No. 4, pp. S616. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 9-14, 1999 Association for Research in Vision and Opthalmology. Language: English.

L84 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
1998:243215 Document No.: PREV199800243215. Adenosine (Ado) mediates vascular endothelial growth in factor (VEGF) induction through A2B Ado receptor (AdoR) in human retinal endothelial cells (HREC. **Grant, M. B. (1)** ; Tarnuzzer, R. W. (1); Caballero, S. (1); Ozeck, M. J.; Shryock, J. C. (1); **Belardinelli, L. (1)**. (1) Dep. Med., Univ. Fla., Gainesville, FL USA. IOVS, (March 15, 1998) Vol. 39, No. 4, pp. S913. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 10-15, 1998 Association for Research in Vision and Ophthalmology. Language: English.

L84 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
1998:291718 Document No.: PREV199800291718. Adenosine (Ado) mediates vascular endothelial growth factor (VEGF) induction through A2B Ado receptor (AdoR) in human retinal endothelial cell (HREC. **Grant, M. B. (1)**; Tarnuzzer, R. W. (1); Caballero, S. (1); Ozeck, M. J.; Shryock, J. C. (1); **Belardinelli, L. (1)**. (1) Dep. Med., Univ. Fla., Gainesville, FL USA. Drug Development Research, (Jan., 1998) Vol. 43, No. 1, pp. 14. Meeting Info.: 6th International Symposium on Adenosine and Adenine Nucleotides: New Frontiers in the 3rd Millennium Ferrara, Italy May 19-24, 1998 ISSN: 0272-4391. Language: English.

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